

FIG. I

SUBSTITUTE SHEET

2/30

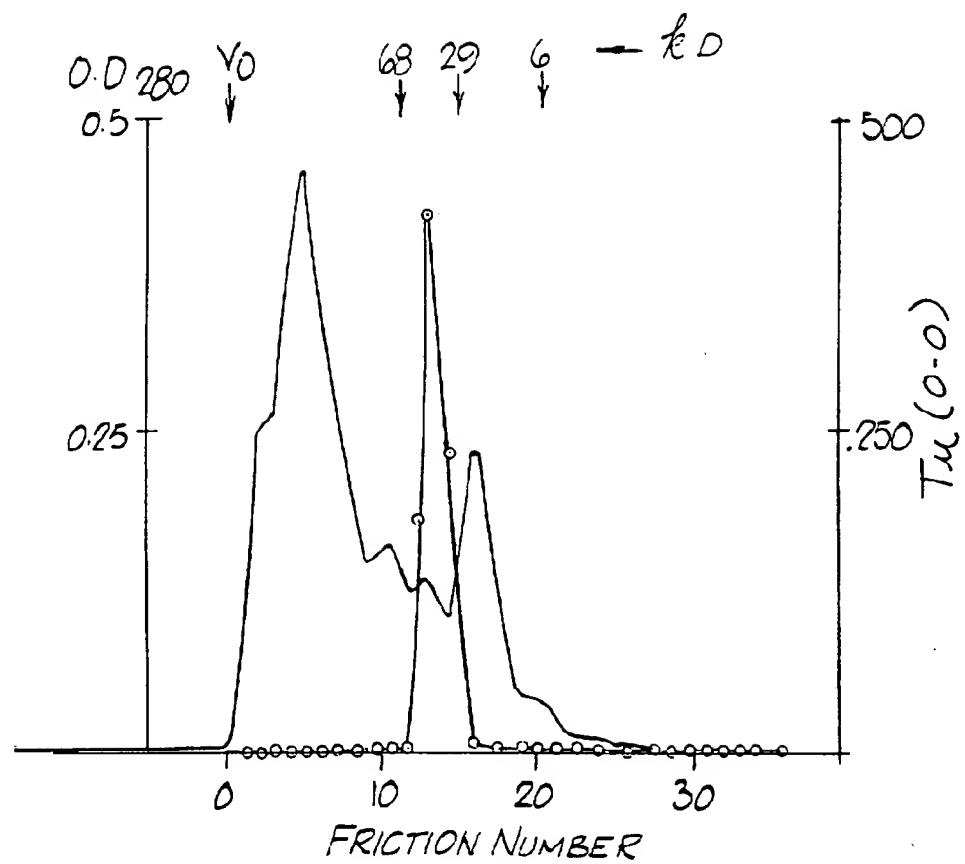
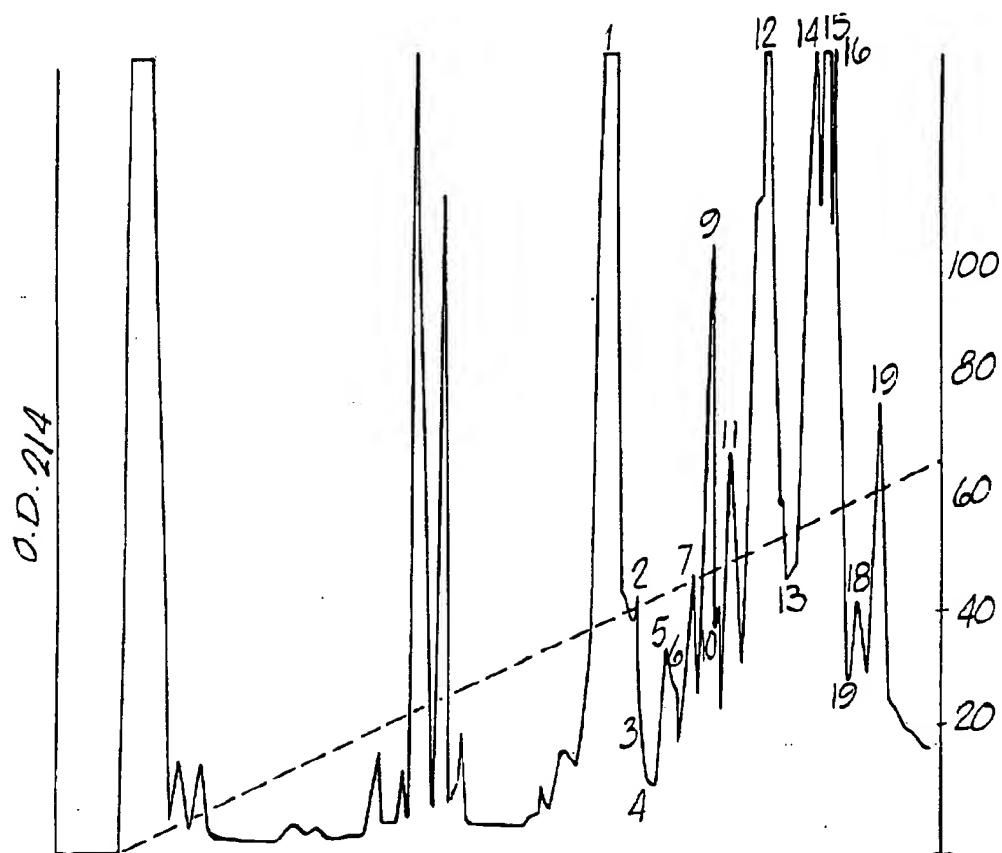


FIG. 2

SUBSTITUTE SHEET



GDNF ACTIVITY IN Tu

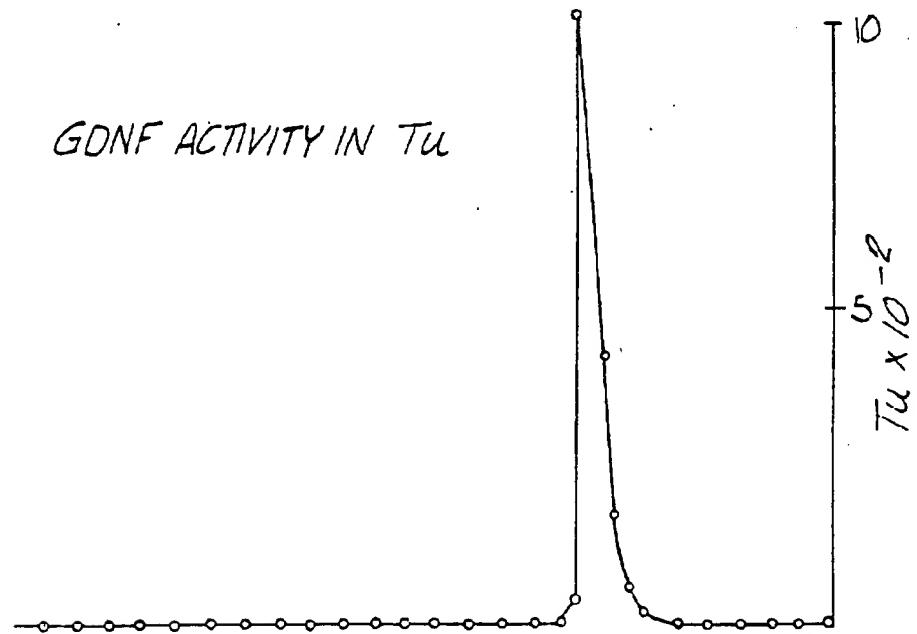


FIG. 3  
SUBSTITUTE SHEET

4 / 30

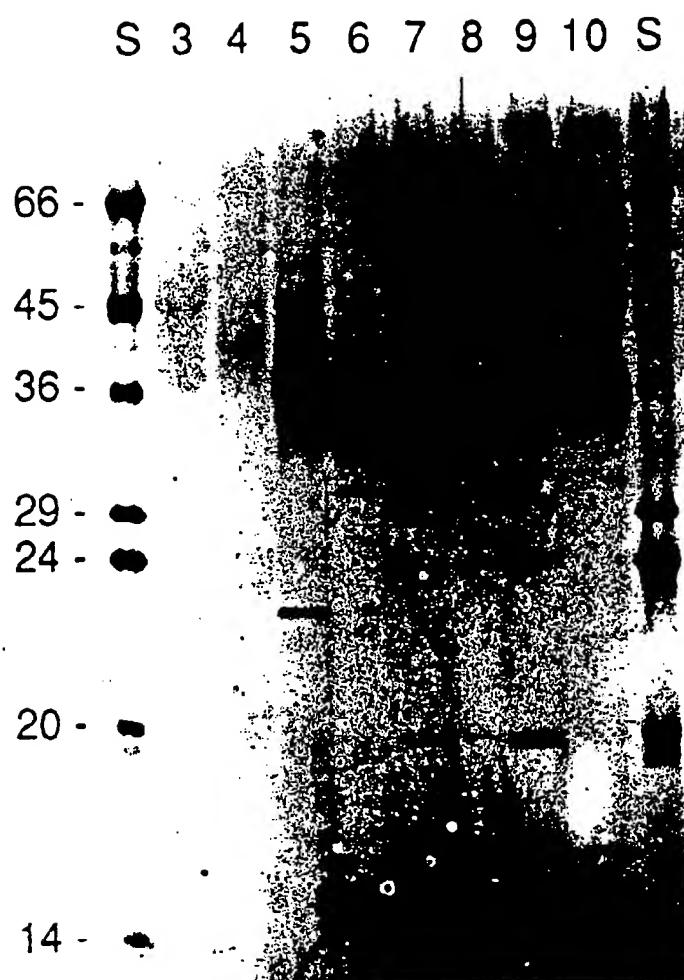


FIG. 4

SUBSTITUTE SHEET

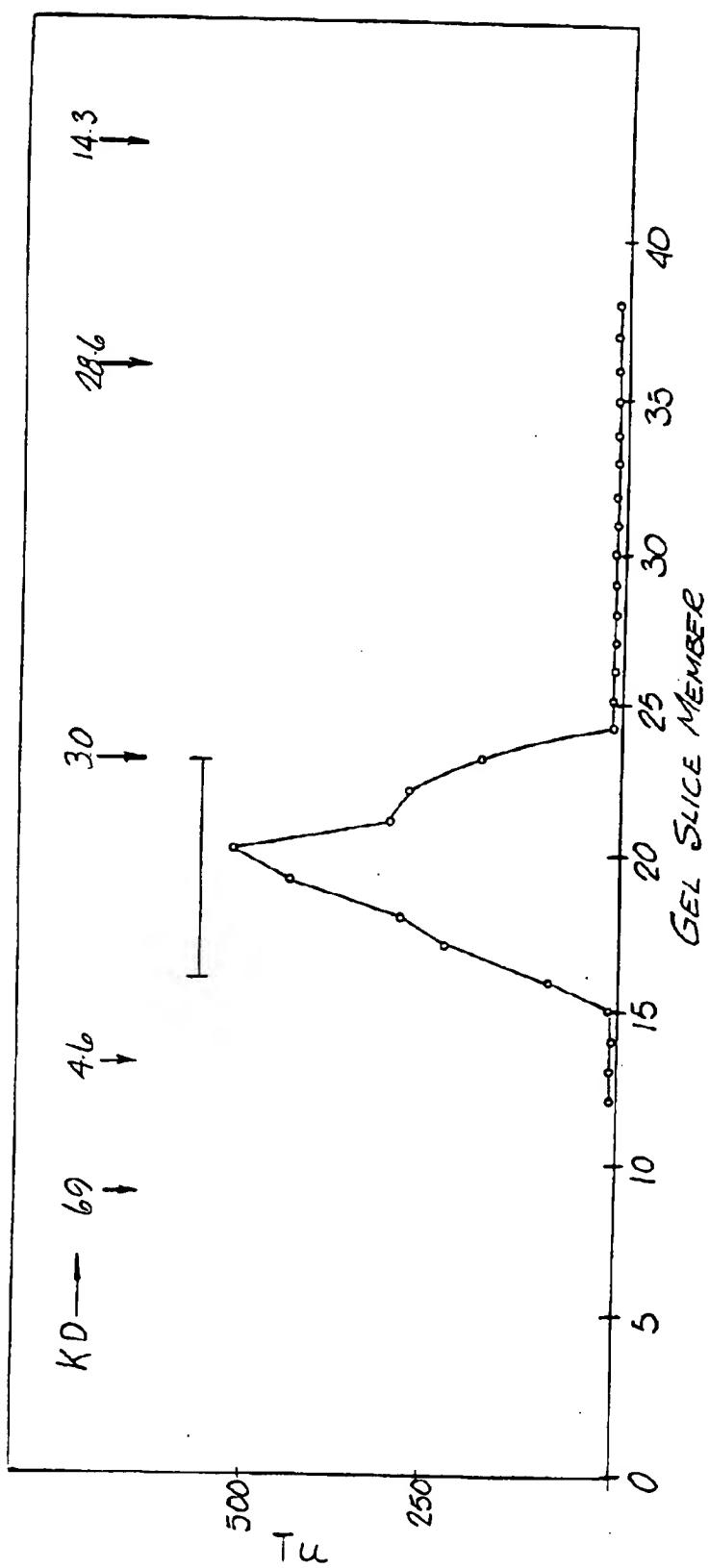


FIG. 5

SUBSTITUTE SHEET

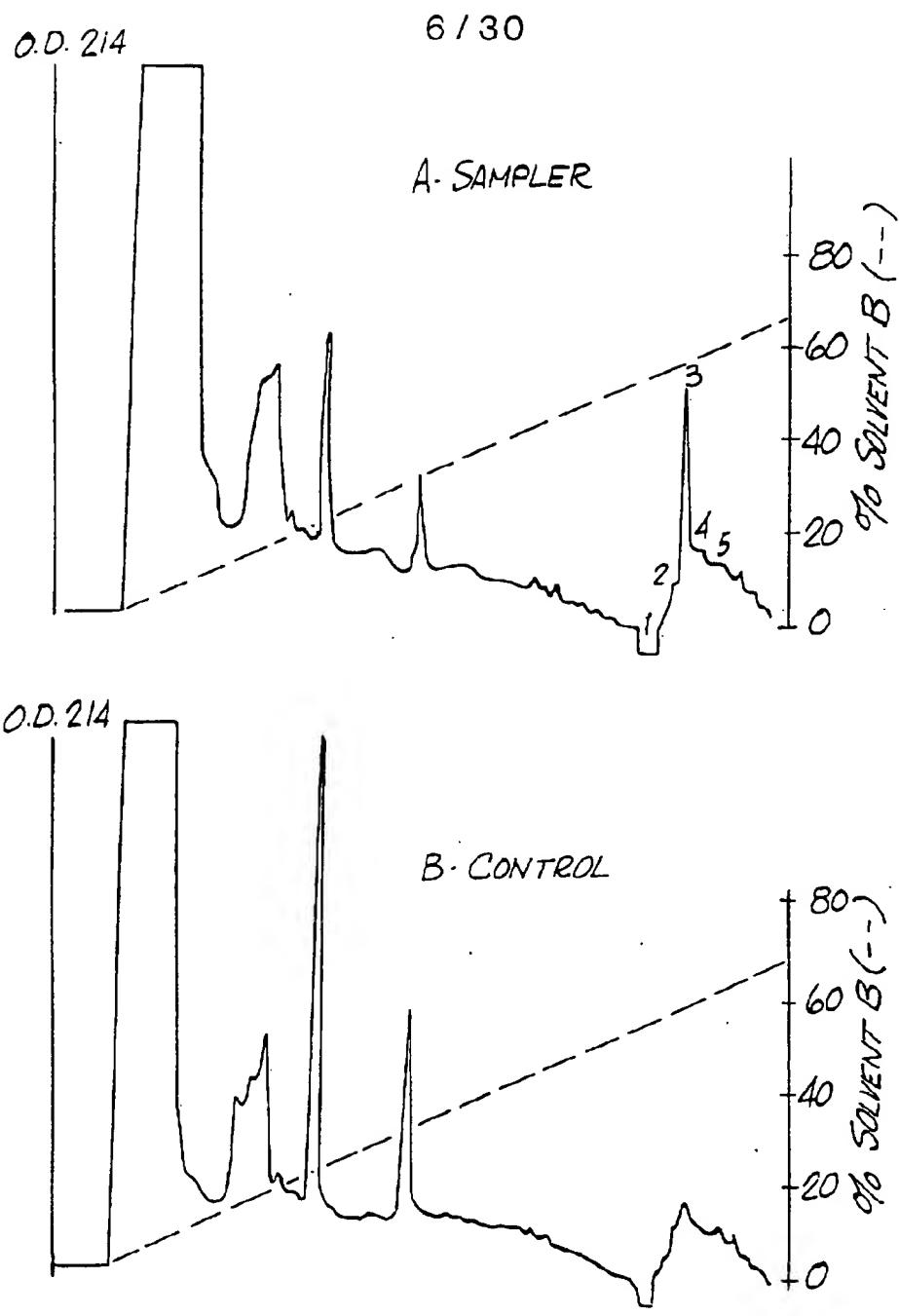


FIG. 6

7 / 30

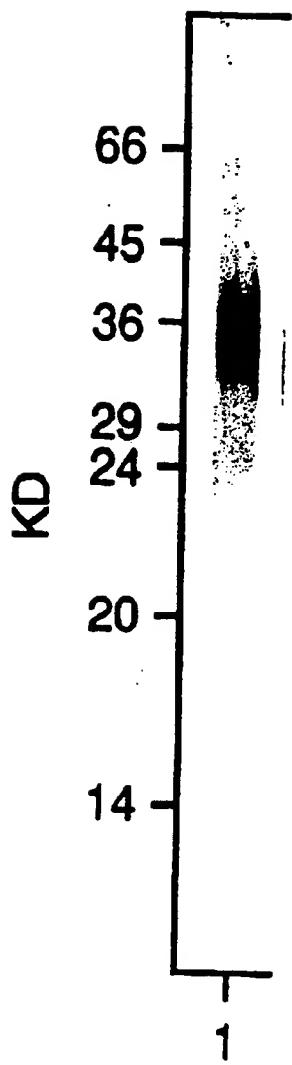


FIG. 7

8 / 30

## FIGURE 8

Amino-terminal sequence of GDNF

(Ser)-Pro-Asp-Lys-Gln-Ala-Ala-Leu-Pro-Arg-Glu-(Arg)-Asn-( )-Gln-Ala-Ala-Ala-(Ser)-Pro-(Asp)-(Asn)

- no residue could be unequivocally identified in this position
- amino acid residues in parenthesis are those identified with less certainty

09/30

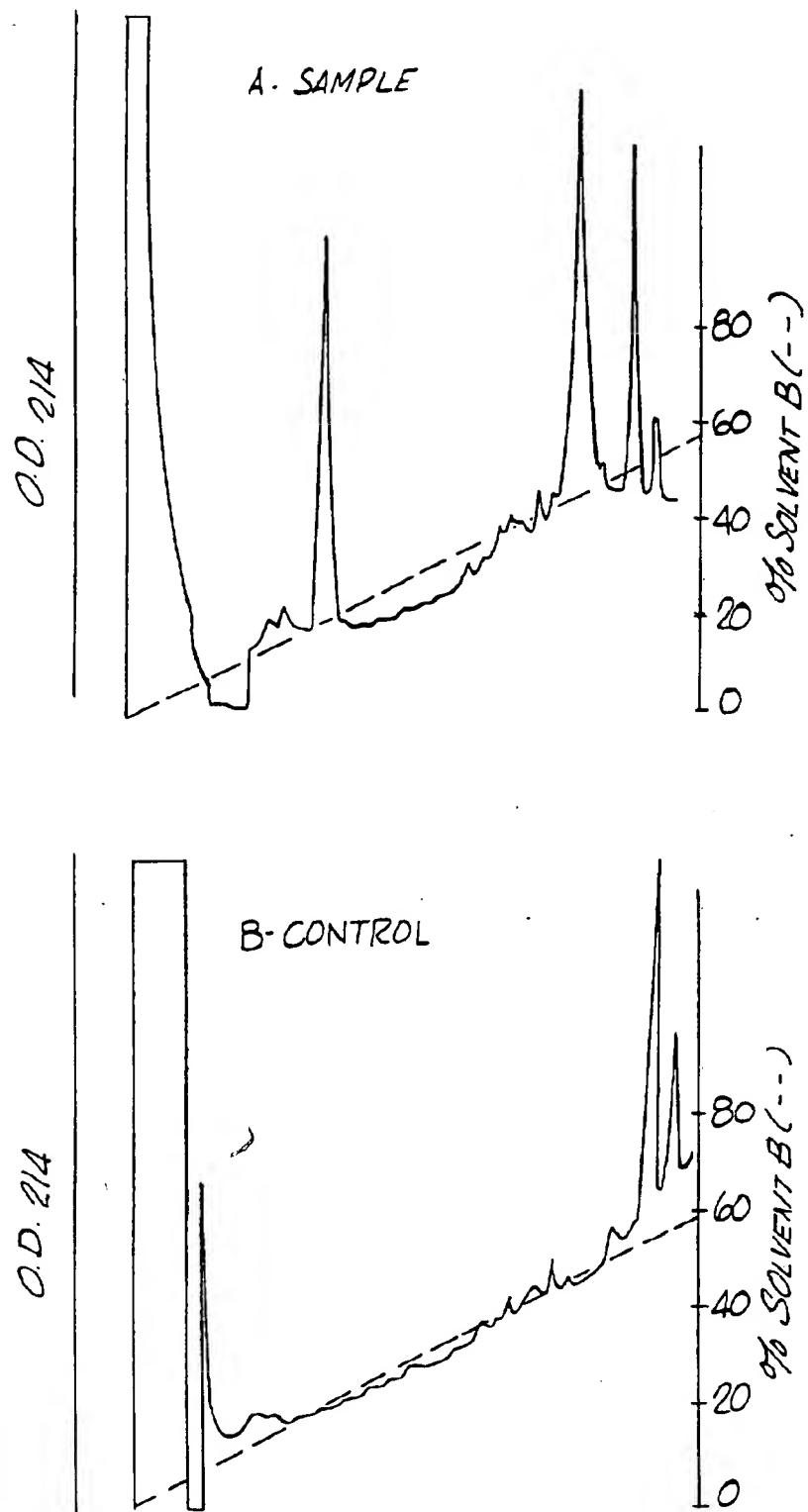


FIG.9  
SUBSTITUTE SHEET

10 / 30

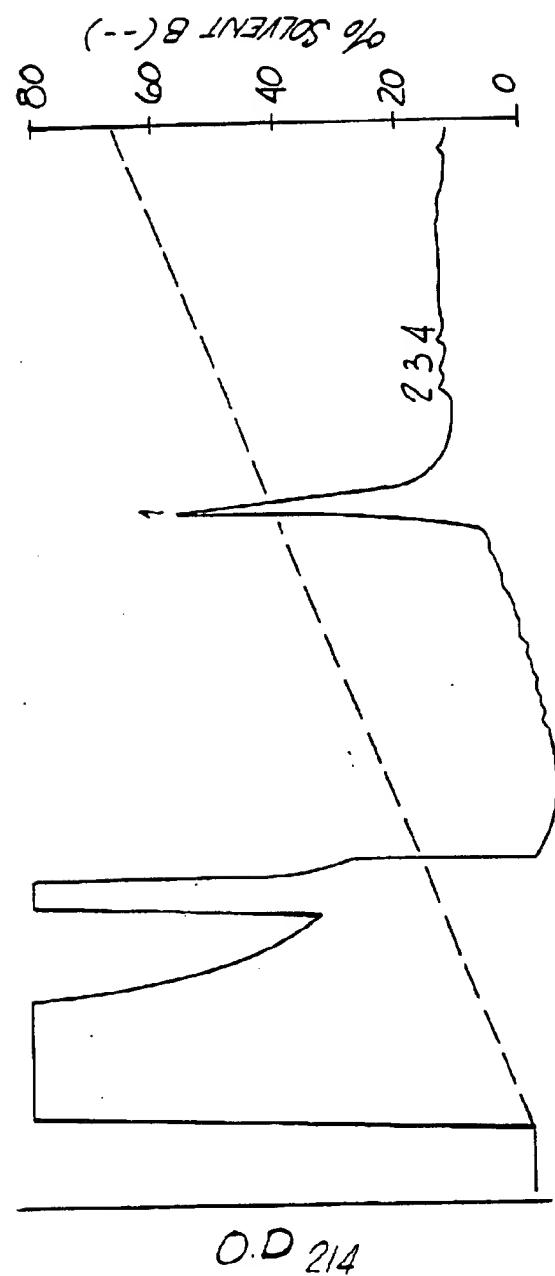


FIG.10

SUBSTITUTE SHEET

11/30

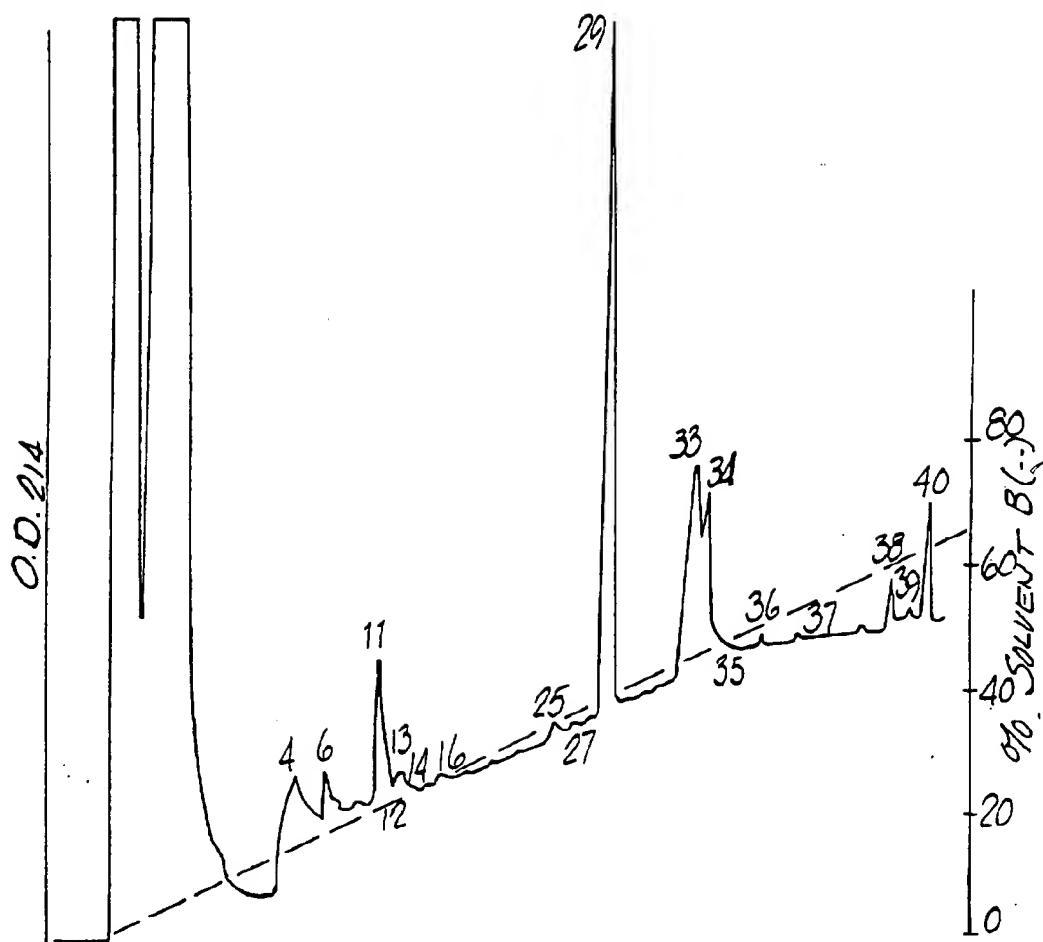


FIG.11

SUBSTITUTE SHEET

**FIGURE 12****An internal sequence of the GDNE**

Asp - (Lys/Gln) - Ile - Lys - Asn - Leu - (Gly) \* - (Arg) - (Val) -  
(Arg) - (Arg) - Leu

\*Amino acid residues placed in parentheses are ones  
identified with less certainty.

13 / 30

**SUBSTITUTE SHEET**

FIG. 13

AGA GCG AAA GGT CCG AGA GGC AGG GGC AAA AAT GGG GGG TGC GTC TTA ACT  
R G K G R R G Q R G K N R G C V L T

GCA ATA CAC TTA AAT GTC ACT GAC TTC GGT GAA GGC TAC GAA ACC AAG GAG GAA  
A I H L N V T D L G L G Y E T K E E

CTG ATC TTC CGA TAT TGT AGC GGT TCC TGT GAA GCG GAG ACA ATG TAC GAC  
L I F R Y C S G S C E A A E T M Y D

AAA ATA CTA AAA AAT CTG TCT CGA AGT AGA AGG CTA ACA AGT GAC AAG GTA GAC  
K I L K N L S R S R R T S D K V G

CAG GCA TGT TGC AGG CCG GTC GCC TTC GAC GAC CTG TCG TTT TTA GAC GAC  
O A C C R P V A F D D D L S F L D D

AGC CTG GTT TAC CAT ATC CTA AGA AGG CAT TCC GCT AAA CGG TGT GGA TGT ATC  
S L V Y H I L R K H S A K R C G C. I

TGA CCCTGGCTCC AGAGACTGCT GTTGATTGCA TTCCTGCTAC AGTGCGAAGA AGGGACCA  
745

GTTCCAGG AAATATTGTC CCAGAAGGAA AGATAAAGGAC CAAGAAGGCA GAGGAGGAGG CGGAAAGAAGA  
815

AGAAGAAG AGGAGCGAAG GCAGCCATCT GTGGGACCT GTAGAAGGAG GCCCAGCTAC AG  
875

FIG 13 (CONT)

## SUBSTITUTE SHEET

FIGURE 14

S	L	R	A	L	P	D	K	Q	A	A	A	E	R	N	R	G	R	A	A	A	A	A	A	E	R	C	N	S	E	T	E	D	G	I
S	L	R	A	L	P	D	K	Q	A	A	A	E	R	N	R	G	R	A	A	A	A	A	A	E	R	C	N	S	E	T	E	D	G	I
S	L	R	A	L	P	D	K	Q	A	A	A	E	R	N	R	G	R	A	A	A	A	A	A	E	R	C	N	S	E	T	E	D	G	I
S	L	R	A	L	P	D	K	Q	A	A	A	E	R	N	R	G	R	A	A	A	A	A	A	E	R	C	N	S	E	T	E	D	G	I
S	L	R	A	L	P	D	K	Q	A	A	A	E	R	N	R	G	R	A	A	A	A	A	A	E	R	C	N	S	E	T	E	D	G	I

**SUBSTITUTE SHEET**

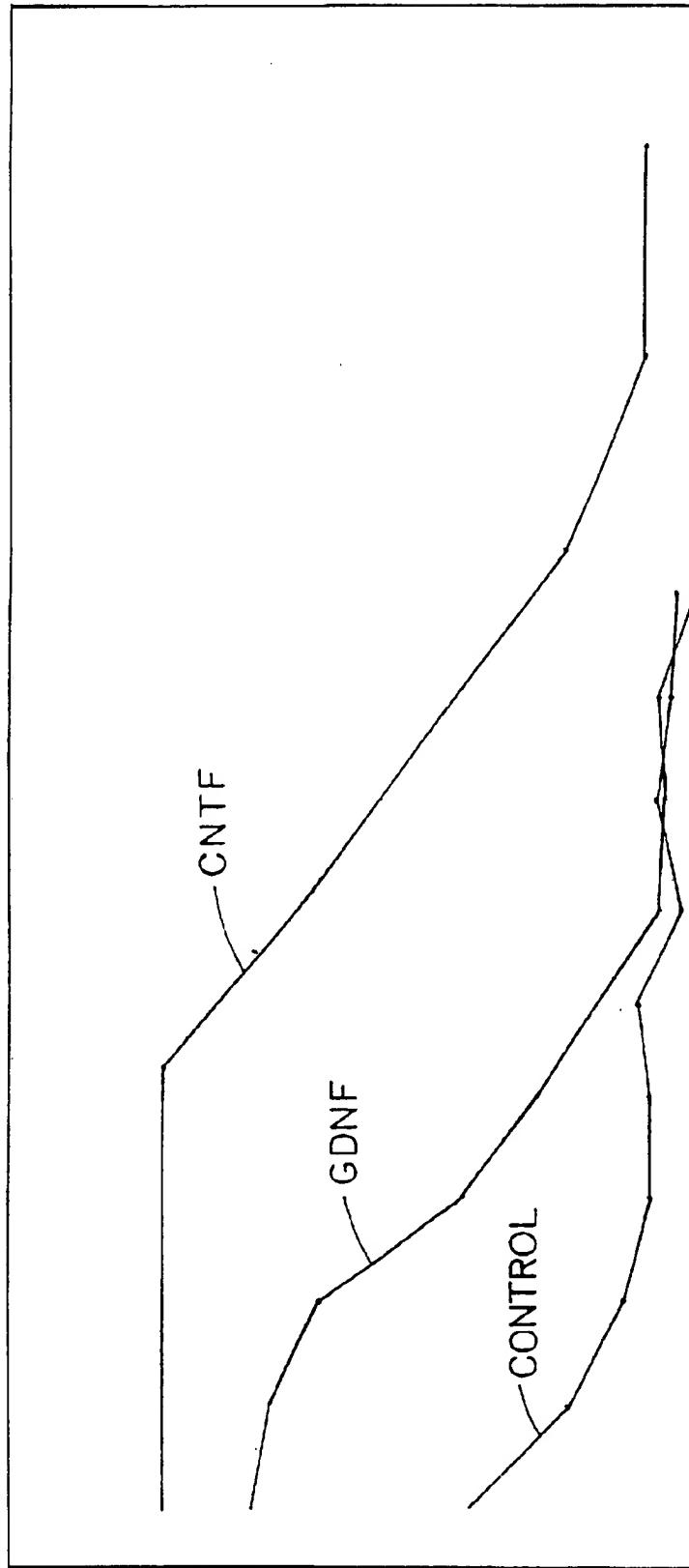


FIG. 15

SUBSTITUTE SHEET

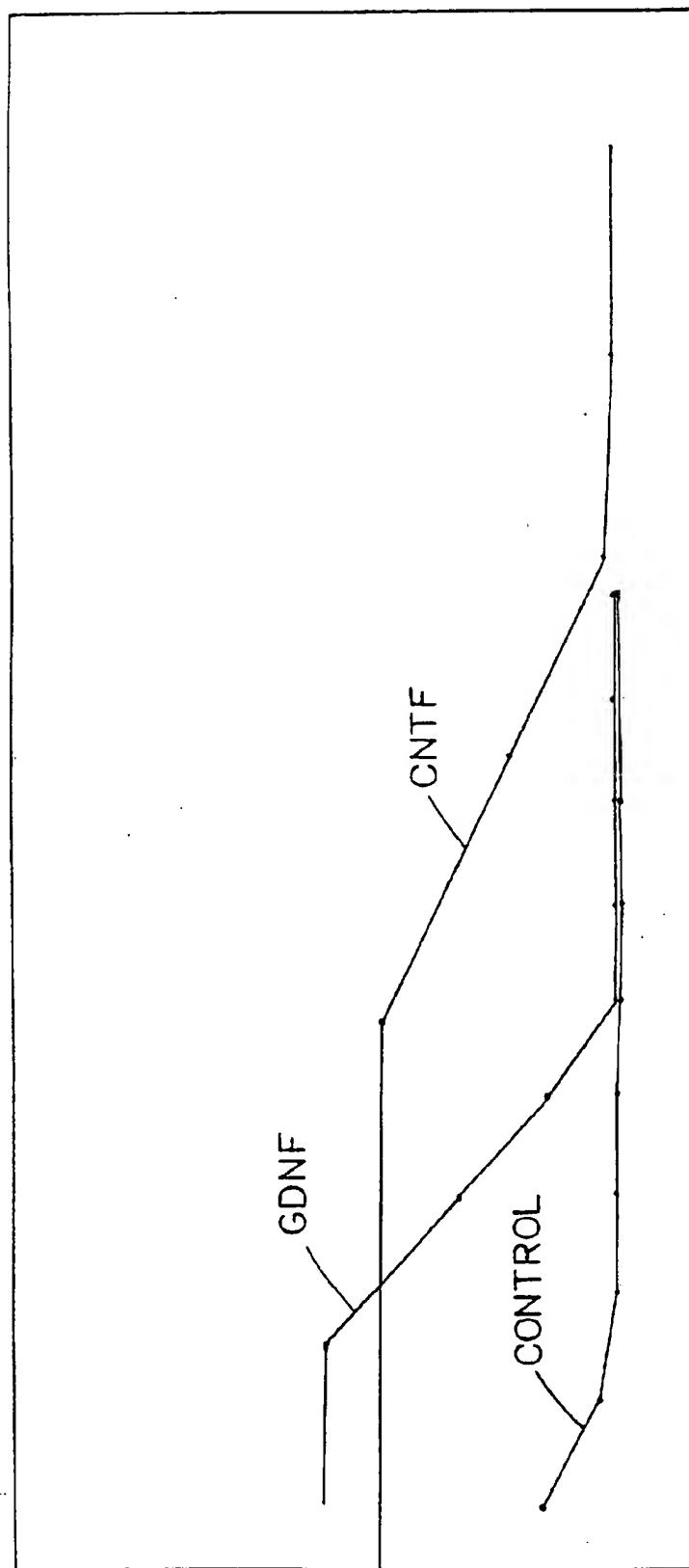


FIG.16

SUBSTITUTE SHEET

18 / 30

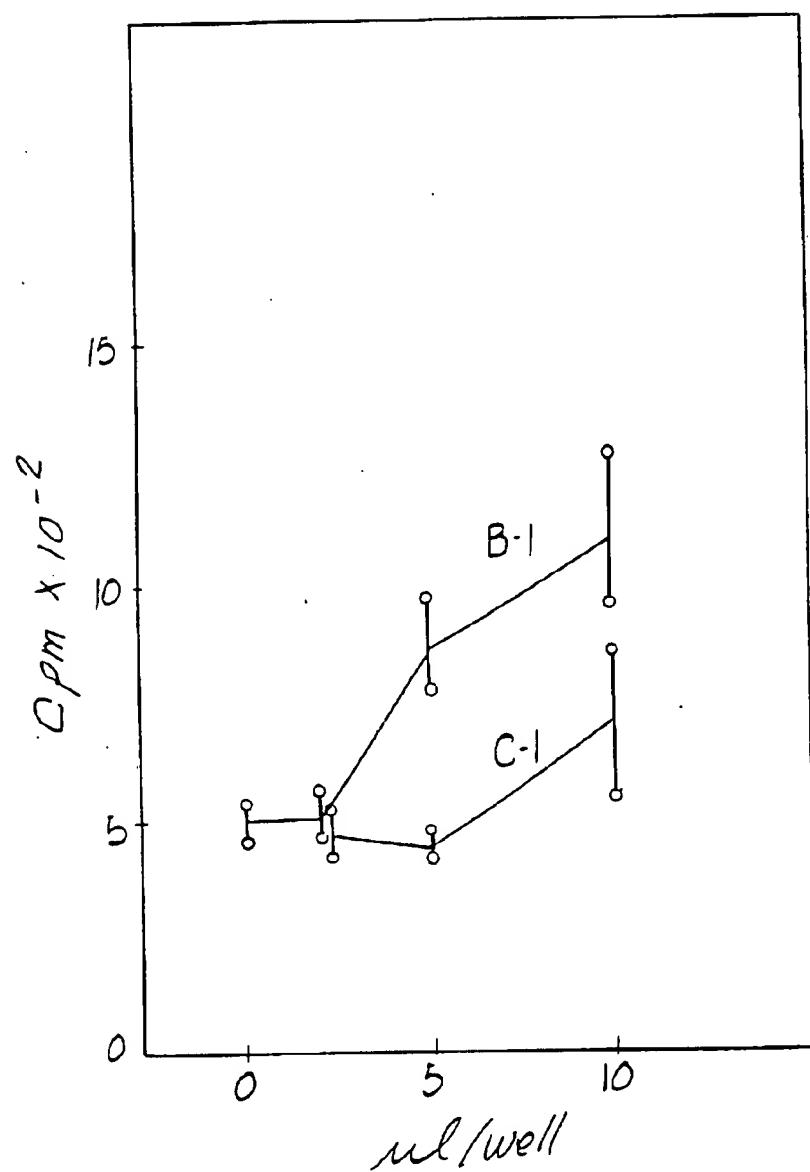


FIG.17

19 / 30

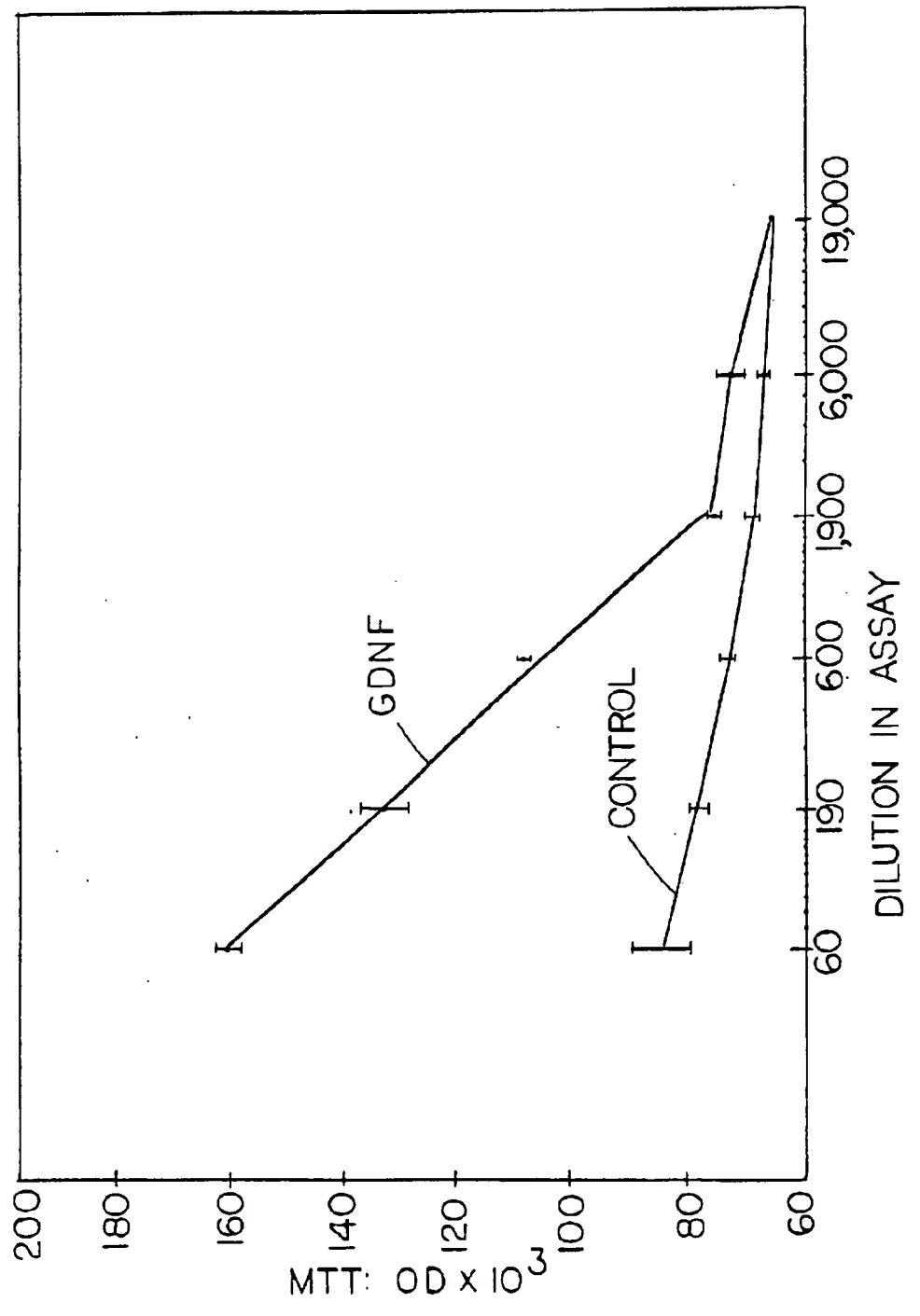


FIG.18

SUBSTITUTE SHEET

131  
GAT TTT ATT CAA GCC ACC ATT AAA AGA CTG MA AGG TCA CCA GAT AAA CAA ATG GCA GTG CTT  
D F I Q A T R K R L K R S P D K Q M A V L

CCT	<u>AGA</u>	<u>GAG</u>	<u>CGG</u>	<u>AAT</u>	<u>CCG</u>	<u>GCA</u>	<u>GCT</u>	<u>GCC</u>	<u>AAC</u>	<u>CCA</u>	<u>GAG</u>	<u>AT</u>	<u>TCC</u>	<u>AGA</u>	<u>AAA</u>	<u>GCT</u>
P	R	R	E	R	N	R	Q	A	A	N	P	E	N	S	R	G

CGG AGA GGC CAG AGG GAC AAA AAC CGG GCT TGT GTC TAA ACT GCA ATA CAT TTA AT GTC ACT  
R R G Q R G K N R G C V L T A I H L N V T

GAC TTC GGT CTG GGC TAT GAA ACC AAG GAG GAA CTG ATT TTC AGG TAC TTC AGC GGC TCT TGC  
D L C L G Y E T K E E L I F R Y C S G S C

<u>A</u>	<u>G</u>	<u>T</u>	<u>C</u>	<u>T</u>	<u>G</u>	<u>A</u>	<u>C</u>	<u>T</u>	<u>T</u>	<u>G</u>	<u>A</u>	<u>T</u>	<u>C</u>	<u>G</u>	<u>T</u>	<u>T</u>	<u>T</u>	<u>A</u>
S	D	K	V	G	Q	A	C	R	P	I	A	F	D	D	L	S	F	L

**SUBSTITUTE SHEET**

FIG. 19

21 / 30

509

GAT	RAC	CIG	GTT	TAC	CAT	ATT	CTA	AGA	AAG	CAT	TCC	GCT	AAA	AGG	TGT	GGA	TGT	TTC	TGA
D	N	L	V	Y	H	I	L	R	K	H	S	A	K	R	C	G	C	I	.

562

ctccggctccaggactgtgttattgtcatttcctgtacatgtcaaagaag

FIG. 19 (CONT)

**SUBSTITUTE SHEET**

22 / 30

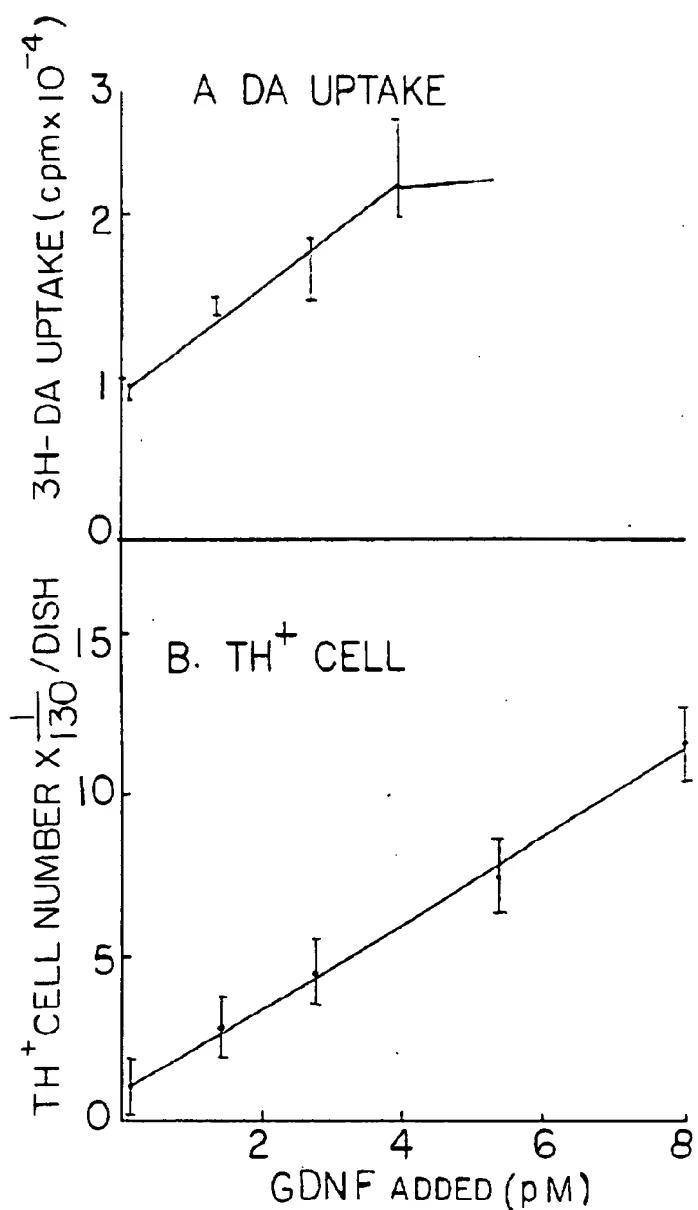


FIG.20

SUBSTITUTE SHEET

23/30

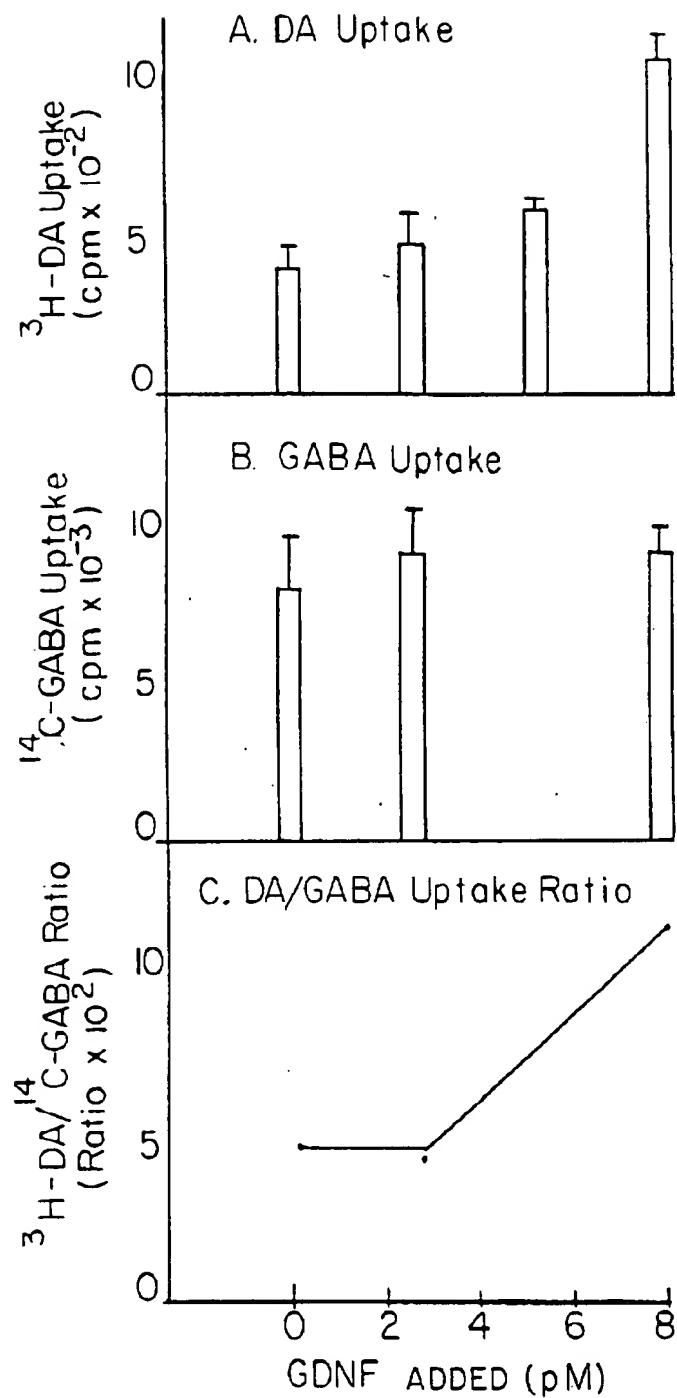


FIG.21

SUBSTITUTE SHEET

4

ttctcccccaccccccgtccccggca ggt gcc gcc gcc  
g a a a

97

ggg ggg gac ttt aag atg aag tta tgg gat gtc  
g r d f k m k l w d v v a v c l v l

151

cgc cac acc gcc tcc gcc tcc ccc ccg ctg ccc ccc gtt gtt agg agg cct ccc gag gag  
l h t a s a f p l a g k r p e a

205

ccc gcc gaa gac ccg tcc ctc ggc ccg ccg ccg ccc ttc gg ctg agg agg  
p a e d r s l g r r a p f a l s s

223

gac tgtaaagaaccgttcc  
d

FIG.22

SUBSTITUTE SHEET

25 / 30

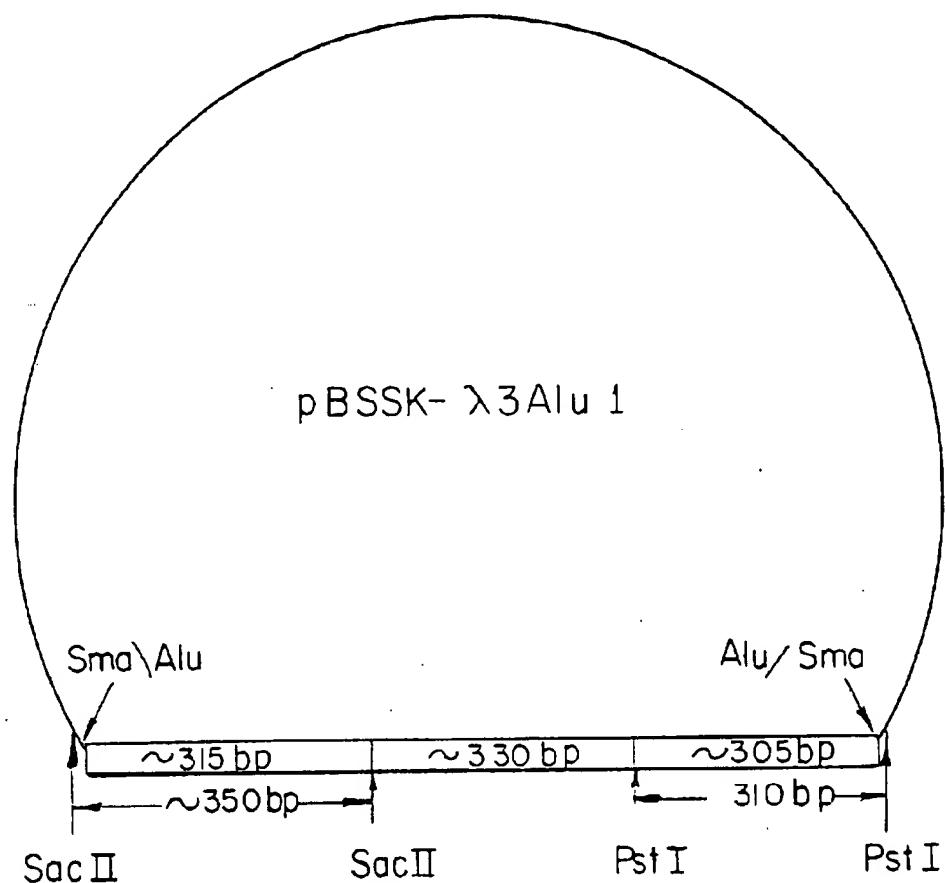


FIG.23

SUBSTITUTE SHEET

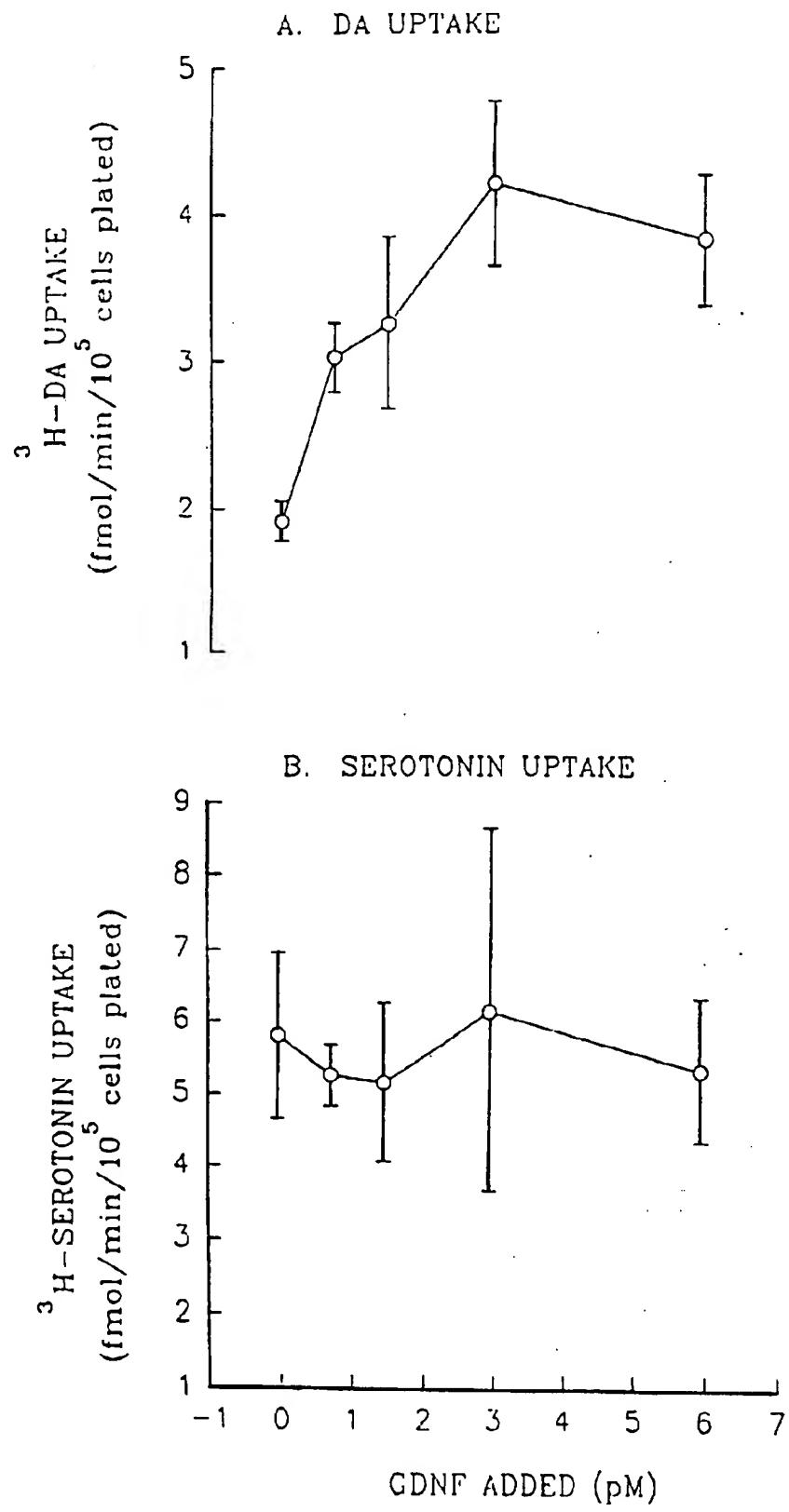


FIG.24  
SUBSTITUTE SHEET

27 / 30

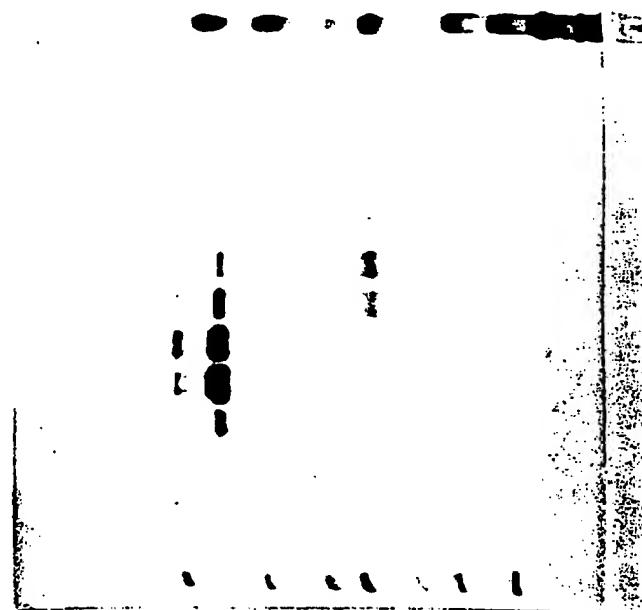


FIG.25

SUBSTITUTE SHEET

28 / 30

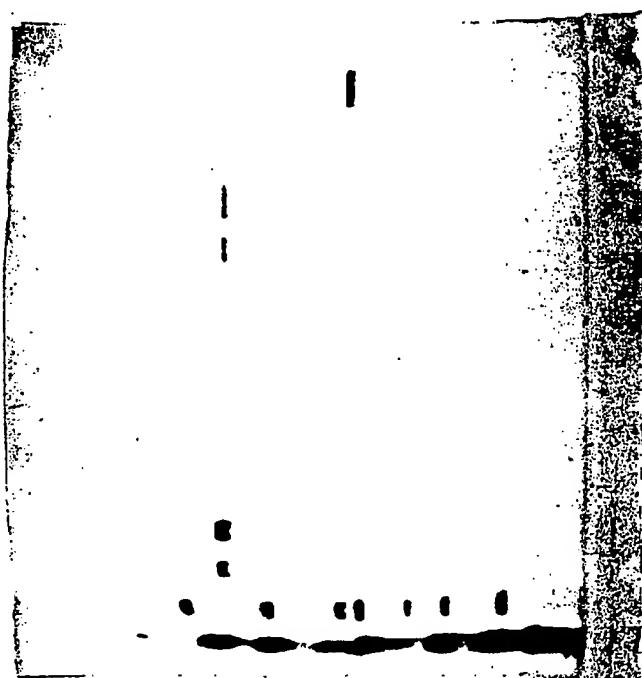
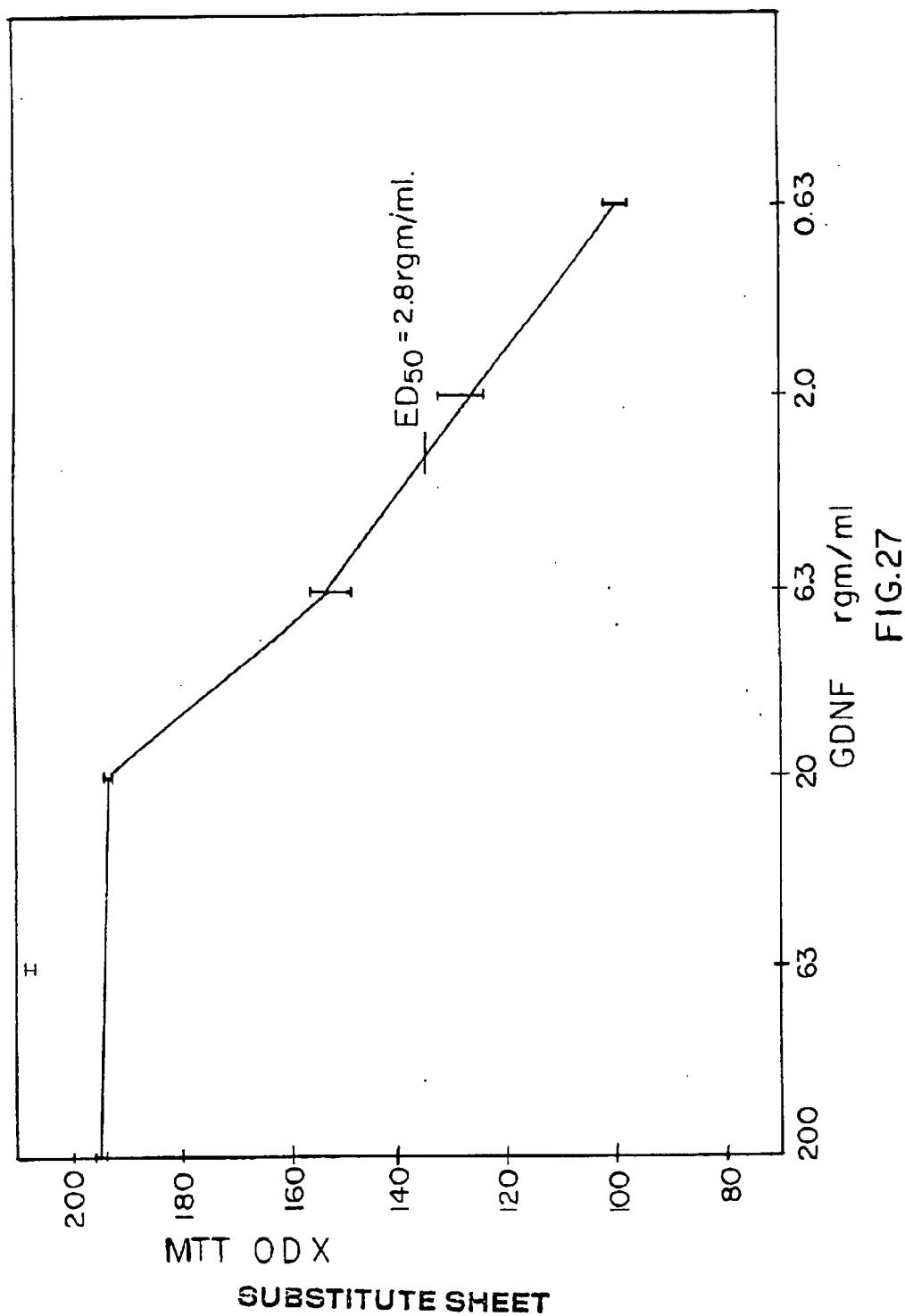


FIG.26

SUBSTITUTE SHEET



SUBSTITUTE SHEET

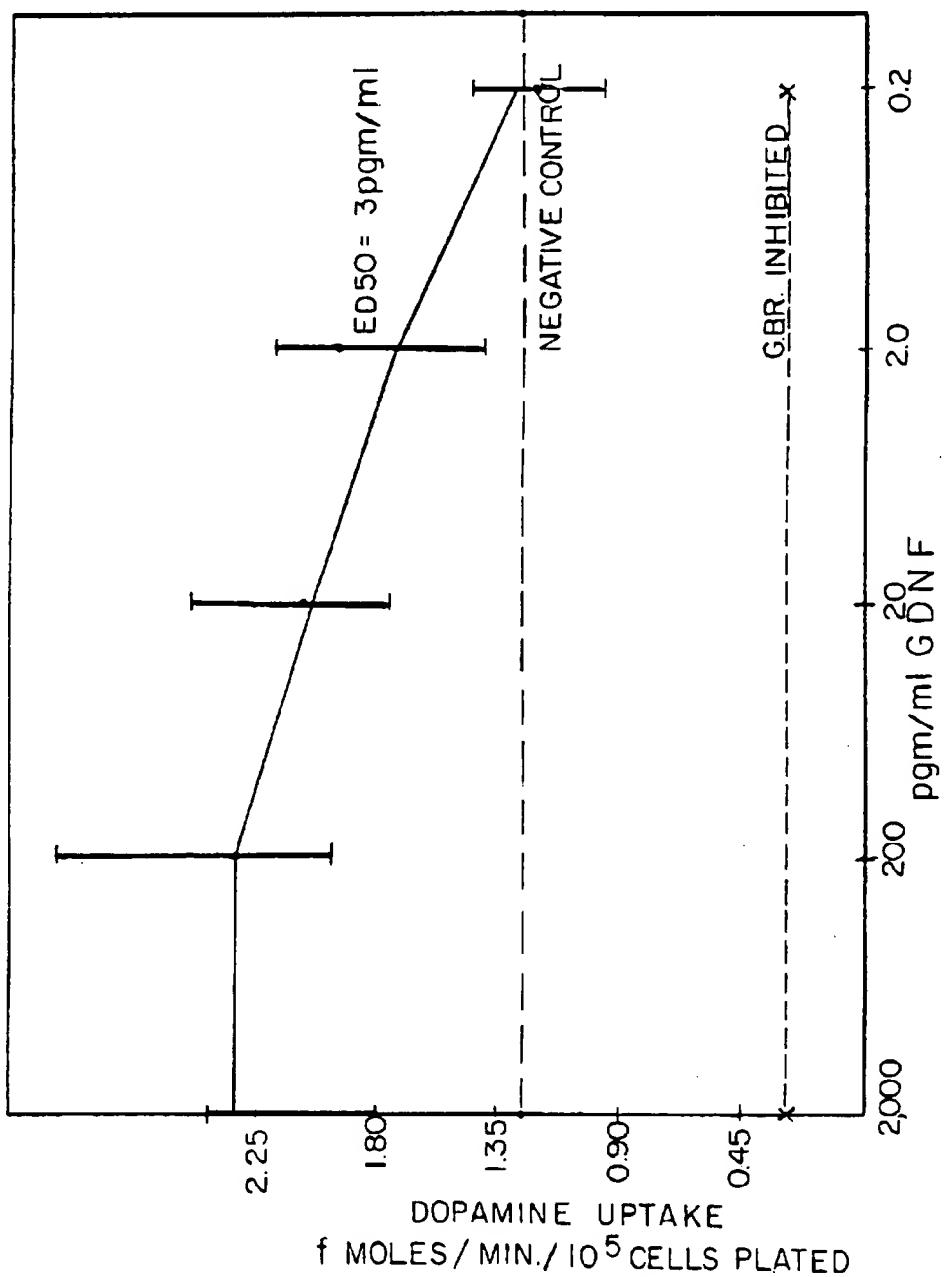


FIG. 28

SUBSTITUTE SHEET

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US92/07888

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(5) :C07H 15/12; C12P 21/06; C12N 1/22; A61K 37/36

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/399, 387, 417; 514/12; 536/27; 435/320.1, 252.3, 69.1; 604/890.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Dialog, search terms: glial cells, glioblastoma, glial-derived, growth factor

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<u>Exp. Cell Res.</u> , Volume 120, No. 1, issued 1980. Norrgren et al., "Release of Nerve Growth Factor By Human Glial Cells in Culture", pages 31-40, see abstract.	1-25, 37-40, 56-74
Y	<u>Bio/Techniques</u> , Volume 1, No. 4, issued 1983. Sofer et al., "Designing an Optimal Chromatographic Purification Scheme for Proteins", pages 198-203, entire document.	1-25
Y	Creighton, "Proteins", published 1984 by Freeman (N.Y.), see pages 39-42	1-25, 37-41, 44-55, 56-59, 60-62
Y	NATURE, Volume 303, issued 30 June 1983. Ullrich et al., "Human beta-Nerve Growth Factor Gene Sequence Highly Homologous to that of Mouse", pages 821-825	26-36, 42-43, 63-69, 44-55, 70-74
Y	BRAIN RESEARCH, Volume 560, issued 1991, Bakhit et al., "Increase in Cilia-Derived Nerve Growth Factor Following Destruction of Hippocampal Neurons", page 76-83.	1-25, 37-41, 56-59, 60-62, 70-74, 63-69

Further documents are listed in the continuation of Box C.  See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be part of particular relevance		
"E" earlier document published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" documents which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 09 December 1992	Date of mailing of the international search report 13 JAN 1993
---	---

Name and mailing address of the ISA/ Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer SHELLY J. GUEST Telephone No. (703) 308-0196
---	---